herein. Support for new claims 48-49 can be found in the specification at, *inter alia*, page 15, lines 4-9 and page 21, line 37 to page 22, line 9. New claims 50-51 have been added herein. Support for new claims 50-51 can be found in the specification at, *inter alia*, original claims 3 and 5. Accordingly, no new matter has been added by these amendments.

The specification has been amended to correct obvious typographical errors. Accordingly, no new matter has been added by these amendments.

Applicant acknowledges that the Restriction Requirement has been made final and that claims 16-30 and 39-45 have been withdrawn from further consideration. Claims 16-30 and 39-45 have been cancelled herein without prejudice or disclaimer of the subject matter contained therein. Claim 1 has also been cancelled herein without prejudice or disclaimer of the subject matter contained therein.

Therefore, after entry of these amendments claims 2-15 and 46-51 will be pending in the application.

The outstanding rejections are addressed individually below.

1. ***Amended claims 1-15 and 46 are definite.***

Claims 1-15 and 46 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite in their recitation of "neuronal and glial properties" because it is unclear what specific properties the claimed cells are required to have.

Claim 1 has been cancelled herein; therefore Applicant respectfully submits that the rejection is moot with respect to this claim.

Furthermore, the remaining claims, which have been amended, do not contain the phrase "neuronal and glial properties." Therefore, Applicant respectfully submits that this rejection has been rendered moot.

Accordingly, Applicant respectfully requests that this rejection be reconsidered and withdrawn.

2. ***Claims 1-15 and 46 are not anticipated under 35 U.S.C. § 102(e).***

Claims 1-15 and 46 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 5,851,832 to Weiss *et al.* (1998) ("the '832 patent"). Applicant respectfully traverses this rejection.

Claim 1 has been cancelled herein; therefore Applicant respectfully submits that the rejection is moot with respect to this claim.

New claim 47 is directed to a non-tumorigenic cell composition derived from embryonic stem cells, containing at least 85% isolated neuronal precursor cells, which have the ability to differentiate to neuronal or glial cells, and no more than 15 % primitive embryonic and non-neural cells.

Claims 2-15, 46 and 48-51, which have been amended or added as described above, are generally directed to such cell compositions, obtainable by performing specified steps, as well as a cell library and a pharmaceutical composition.

The cell compositions of the present invention are derived from embryonic stem cells. The specification defines embryonic stem cells in the specification at page 6, line 35 to page 7, line 2, which states

> Embryonic stem cells. These cells can be isolated from early embryos at the blastocyst stage. They represent pluripotent cells which can generate all tissues and cell types. In cell culture they can be maintained in a pluripotent stage over many passages. ES cells can also be obtained through nuclear transplantation, i.e. transplantation of cell nuclei into enucleated oocytes and subsequent culture to the blastocyst stage. The definition of *ES cells* also includes ES cell-like cells obtained from embryonic germ cells.

In contrast, the '832 patent states that "the cells proliferated using the methods described in Examples 1-4 are termed 'neural stem cells'. A neural stem cell is an undifferentiated neural cell that can be induced to proliferate using the methods of the present invention." (emphasis added) (Col. 12, lines 51-55) The '832 patent further

states that "[m]ultipotent neural stem cells can be obtained from embryonic, post-natal, juvenile or adult neural tissue." (emphasis added) (Col. 13, lines 13-15)

Furthermore, the cell composition of the present invention differs from the cells in the '832 patent, which are directly obtained from the nervous system, since it comprises also primitive embryonic and non-neural cells.

The precursor cells according to the present application develop in a different manner compared to the precursor cells of the nervous system. Different *in vitro* conditions are responsible for variable features of the ES-cell derived precursor cells. The ES-cell derived precursor cells have never been in the living organism and are therefore never exposed to regional specific or cell-type specific influences. One of skill in the art would be aware that the contact with embryonic and non-neural cells, as well as the non-physiological exposure to growth factors over weeks, causes fundamental changes in the regulation mechanisms of the *in vitro* generated cells of the present invention. Thus, the cell compositions of the present invention differ from those of the '832 patent.

Therefore, Applicant submits that in view of the foregoing remarks and the references submitted, pending claims 2-15 and 46-51 are not anticipated by the '832 patent.

Accordingly, Applicant respectfully requests that the rejection of these claims under 35 U.S.C. § 102(e), be reconsidered and withdrawn.

CONCLUSIONS

In view of the arguments set forth above, Applicant respectfully submits that the rejections contained in the final Office Action mailed on June 5, 2002, have been overcome, and that the claims are in condition for allowance. If the Examiner believes that any further discussion of this communication would be helpful, she is invited to contact the undersigned at the telephone number provided below.

Applicant encloses herewith a Petition for a Three Month Extension of Time pursuant to 37 C.F.R. § 1.136 up to and including December 5, 2002, to respond to the Examiner's Office Action mailed on June 5, 2002. Please charge deposit account no. 08-0219 the $460.00 fee (small entity) for this purpose.

No other fees are believed to be due in connection with this response. However, please charge any underpayments or credit any overpayments to Deposit Account No. 08-0219.

Respectfully submitted,

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Date: December 5, 2002

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Attachments: Compare Copy of Amendments to Specification
Clean Copy of Pending Claims
Compare Copy of Claims

Compare Copy of Amendments to Specification
USSN 09/581,890
Filed August 28, 2000

Paragraph on page 4, lines 21-31:

The generation of sufficient numbers of defined neural precursor cells is currently one of the key problems in neural transplantation. At present, precursor cells are isolated from the embryonic mammalian brain. For example, material from up to seven human embryos is required for transplantation of an individual Parkinson patient. Such a strategy is associated with severe problems and cannot be used to treat large numbers of Parkinson patients in the long term. Efforts to proliferate neural cells in vitro prior to transplantation have, so far, not lead to significant improvements. Oncogene-mediated immortalization bears considerable risks due to the introduction of a tumorigenic gene into the donor cells. The order of magnitude of growth factor-mediated proliferation of precursor cells in not sufficient for a potential clinical application. In addition, the ability of expanded cells to incorporate into the host tissue is currently unclear.

Paragraph on page 18, lines 4-9:

The differentiation of the ES cell-derived glial precursors can be influenced by addition of single factors. Addition of CNTF (ciliary neurotrophic factors) shortly before and~~und~~ during growth factor withdrawal will promote astrocytic differentiation. Addition of the thyroid hormone T3 during this stage will result in enhanced differentiation of oligodendrocytes. Addition of serum-containing media during or after growth factor treatment results in a strong increase in the number of astrocytic cells in these cultures.

Clean Copy of Pending Claims
USSN 09/581,890
Filed August 28, 2000

1. Cancelled.

2. (Once Amended) A non-tumorigenic cell composition derived from embryonic stem cells, the composition comprising from 85% to 100% isolated neuronal precursor cells, which have the ability to differentiate to neuronal or glial cells, and from 0% to 15% primitive embryonic and non-neural cells,

the composition being obtainable by:

(a) culturing the embryonic stem cells to produce neural precursor cells,

(b) culturing the neural precursor cells from (a) in a first growth factor-containing serum-free medium,

(c) culturing the cells from (b) in a second growth factor-containing serum-free medium, and

(d) culturing the cells from (c) in a third growth factor-containing serum-free medium,

wherein the cells from (d) have the ability to differentiate to neuronal or glial cells.

3. (Once Amended) The cell composition according to claim 2, wherein the embryonic stem cells in step (a) are in the form of cell aggregates.

4. (Once Amended) A non-tumorigenic cell composition derived from embryonic stem cells, the composition comprising from 85% to 100% isolated neuronal precursor cells, which have the ability to differentiate to neuronal or glial cells, and from 0% to 15% primitive embryonic and non-neural cells,

the composition being obtainable by:

(a) culturing the embryonic stem cells to produce neural precursor cells,

(b) culturing the neural precursor cells from (a) in a first growth factor-containing serum-free medium,

(c) culturing the cells from (b) in a second growth factor-containing serum-free medium to produce neural spheres, and

(d) culturing the neural spheres from (c) in a third growth factor-containing medium to produce a monolayer of glial precursor cells,

wherein the cells of the monolayer have the ability to differentiate to glial cells.

B3 Cont

5. (Once Amended) The cell composition according to claim 4, wherein the embryonic stem cells in step (a) are in the form of cell aggregates.

6. (Twice Amended) The cell composition according to claim 2, wherein said cells grow as a monolayer.

7. (Twice Amended) The cell composition according to claim 2, wherein said cells grow as neural spheres.

8. (Twice Amended) The cell composition according to claim 2, comprising cells with neuronal, astroglial or oligodendroglial properties, or a combination thereof.

9. (Twice Amended) The cell composition according to claim 2, wherein the embryonic stem cells are obtained after nuclear transfer into oocytes.

10. (Twice Amended) The cell composition according to claim 2, wherein the embryonic stem cells are obtained from embryonic germ cells.

11. (Twice Amended) The cell composition according to claim 2, wherein the cells are mammalian cells.

12. (Once Amended) The cell composition according to claim 11, wherein the cells are isolated from a mammal selected from the group consisting of mouse, rat, hamster, pig, cow, primate, and human.

13. (Twice Amended) The cell composition according to claim 2, wherein the cells are genetically modified.

14. (Twice Amended) The cell composition according to claim 2, wherein the cells are frozen.

15. (Twice Amended) Cell library comprising autologous and non-autologous cells according claim 47.

16. Cancelled.

17. Cancelled.

18. Cancelled.

19. Cancelled.

20. Cancelled.

21. Cancelled.

22. Cancelled.

23. Cancelled.

24. Cancelled.

25. Cancelled.

26. Cancelled.

27. Cancelled.

28. Cancelled.

29. Cancelled.

30. Cancelled.

31. Cancelled

32. Cancelled

33. Cancelled

34. Cancelled

35. Cancelled

36. Cancelled

37. Cancelled

38. Cancelled

39. Cancelled.

40. Cancelled.

41. Cancelled.

42. Cancelled.

43. Cancelled.

44. Cancelled.

45. Cancelled.

B4

46. (Once Amended) A pharmaceutical composition comprising the precursor cells of claim 47.

B5

47. (New) A non-tumorigenic cell composition derived from embryonic stem cells, the composition comprising from 85% to 100% isolated neuronal precursor cells, which have the ability to differentiate to neuronal or glial cells, and from 0% to 15% primitive embryonic and non-neural cells.

48. (New) The cell composition of claim 2, wherein the embryonic stem cells in (a) are cultured in serum-free medium.

B5

49. (New) The cell composition of claim 4, wherein the embryonic stem cells in (a) are cultured in serum-free medium.

50. (New) The cell composition of claim 3, wherein the cell aggregates are embryoid bodies.

51. (New) The cell composition of claim 5, wherein the cell aggregates are embryoid bodies.

Compare Copy of Pending Claims
USSN 09/581,890
Filed August 28, 2000

1. Cancelled.

2. (Once Amended) ~~Isolated, purified and~~**A** non-tumorigenic ~~precursor cells with neuronal and glial properties, obtained~~**cell composition derived** from embryonic stem cells**, the composition comprising from 85% to 100% isolated neuronal precursor cells, which have the ability to differentiate to neuronal or glial cells,** and ~~containing no more than~~**from 0% to** 15% primitive embryonic and non-neural cells,

the composition being obtainable by**:**

(a) ~~proliferation of ES~~**culturing the embryonic stem cells to produce neural precursor** cells,

(b) ~~cultivation of~~**culturing** the ~~ES~~**neural precursor** cells from (a) ~~into neural precursor cells~~**in a first growth factor-containing serum-free medium**,

(c) ~~proliferation of~~**culturing** the ~~neural precursor~~ cells **from (b)** in **a second** growth factor-containing serum-free medium, **and**

(d) ~~proliferation of~~**culturing** the ~~neural precursor~~ cells from (c) in ~~another~~**a third** growth factor-containing serum-free medium ~~and isolation of the purified neural precursor cells~~, ~~and~~

~~(e) proliferation of~~

wherein the ~~neural precursor~~ cells from (d) ~~in another growth factor containing serum-free medium and isolation of the purified precursor~~**have the ability to differentiate to neuronal or glial** cells ~~with neuronal or glial properties~~.

3. (Once Amended) ~~Cells~~**The cell composition** according to claim 2, wherein the ~~ES~~ **embryonic stem** cells in **step** (a) are ~~proliferated to~~**in the form of** cell aggregates~~, particularly embryoid bodies~~.

4. (Once Amended) ~~Isolated, purified and~~A non-tumorigenic ~~precursor cells with neuronal and glial properties, obtained~~**cell composition derived** from embryonic stem cells, ~~containing no more than~~**the composition comprising from 85% to 100% isolated neuronal precursor cells, which have the ability to differentiate to neuronal or glial cells, and from 0% to** 15% primitive embryonic and non-neural cells,

the composition being obtainable by:

(a) culturing the embryonic stem cells to produce neural precursor cells,

(b) culturing the neural precursor cells from (a') ~~proliferation of ES cells~~

~~(b') cultivation of the ES cells from (a') into neural precursor cells~~ **in a first growth factor-containing serum-free medium,**

~~(c') proliferation of the neural precursor cells in growth factor containing serum free medium,~~

(c) ~~(d') proliferation of~~**culturing** the ~~neural precursor~~ cells from (~~c'~~**b**) in ~~another~~**a second** growth factor-containing serum-free medium to ~~neural spheres and isolation of the~~**produce** neural spheres, and

(d) ~~(e') proliferation of~~**culturing** the neural spheres from (~~d'~~**c**) in **a third** growth factor-containing medium ~~until generation of~~**to produce** a monolayer of glial precursor cells ~~and isolation of the purified precursor cells with glial properties.~~,

wherein the cells of the monolayer have the ability to differentiate to glial cells.

5. (Once Amended) ~~Cells~~**The cell composition** according to claim 4, wherein the ~~ES~~ **embryonic stem** cells in **step** (a') are ~~proliferated to~~**in the form of** cell aggregates~~, particularly embryoid bodies~~.

6. (Twice Amended) ~~Cells~~**The cell composition** according to claim ~~2~~**2,** wherein said cells grow as **a** monolayer.

7. (Twice Amended) ~~Cells~~**The cell composition** according to claim 2, wherein said cells grow as neural spheres.

8. (Twice Amended) ~~Cells~~**The cell composition** according to claim 2, comprising cells with neuronal, astroglial ~~and/~~or oligodendroglial properties**, or a combination thereof**.

9. (Twice Amended) ~~Cells~~**The cell composition** according to claim 2, wherein the ~~ES~~**embryonic stem** cells ~~were~~**are** obtained after nuclear transfer into oocytes.

10. (Twice Amended) ~~Cells~~**The cell composition** according to claim 2, wherein the ~~ES~~**embryonic stem** cells ~~were~~**are** obtained from embryonic germ cells.

11. (Twice Amended) ~~Cells~~**The cell composition** according to claim 2, wherein the cells are mammalian cells.

12. (Once Amended)~~Cells~~**The cell composition** according to claim 11, wherein the cells ~~were~~**are** isolated from **a mammal selected from** the group ~~comprising~~**consisting of** mouse, rat, hamster, pig, cow, primate, and human.

13. (Twice Amended) ~~Cells~~**The cell composition** according to claim 2, wherein the cells ~~were~~**are** genetically modified.

14. (Twice Amended) ~~Cells~~**The cell composition** according to claim 2, wherein the cells are ~~in a~~ frozen ~~condition~~.

15. (Twice Amended) Cell library comprising autologous and non-autologous cells according claim ~~1~~**47.**

16. Cancelled.

17. Cancelled.

18. Cancelled.

19. Cancelled.

20. Cancelled.

21. Cancelled.

22. Cancelled.

23. Cancelled.

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37. Cancelled

38. Cancelled

39. Cancelled.

40. Cancelled.

41. Cancelled.

42. Cancelled.

43. Cancelled.

44. Cancelled.

45. Cancelled.

46. (Once Amended) A pharmaceutical composition comprising the precursor cells of claim ~~1~~ **47.**

47. **(New) A non-tumorigenic cell composition derived from embryonic stem cells, the composition comprising from 85% to 100% isolated neuronal precursor cells, which have the ability to differentiate to neuronal or glial cells, and from 0% to 15% primitive embryonic and non-neural cells.**

48. **(New) The cell composition of claim 2, wherein the embryonic stem cells in (a) are cultured in serum-free medium.**

49. **(New) The cell composition of claim 4, wherein the embryonic stem cells in (a) are cultured in serum-free medium.**

50. **(New) The cell composition of claim 3, wherein the cell aggregates are embryoid bodies.**

51. **(New) The cell composition of claim 5, wherein the cell aggregates are embryoid bodies.**